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Kawasaki Syndrome

Zespół Kawasaki

INTRODUCTION

Kawasaki syndrome (KS) was described by Tomisaku Kawasaki in 1967 when he reported his 7 years' experience with 50 children who manifested a distinctive clinical illness (1). KS was originally named mucocutaneous lymph node syndrome and was thought to be a benign childhood illness. In the late 1970's about 10 fatal cases of the disease, all in children under 2 years of age, occurred in Japan. Kawasaki's original report in English was followed by Melish's report who described the same illness in 16 children in Hawaii (2, 3). Because of the availability of echocardiography, it is now known that about 20% of untreated patients with KS develop cardiovascular sequelae, from asymptomatic coronary artery ectasia or aneurysm formation to giant coronary artery aneurysm with thrombosis, myocardial infraction and sudden death.

More than 105,000 cases of KS have nowe been recognized in Japan. There were about 4,900 discharge diagnoses of KS over the period of 1984 to 1987 at the U.S. children's hospitals (4). KS has replaced acute rheumatic fever as the leading cause of acquired heart disease in children in the U.S. and its incidence appears to be increasing both in Japan and in the U.S. (4, 5).

CLINICAL PICTURE

In the absence of a diagnostic test for KS, the diagnosis is established by the presence of fever and at least four of five other principal clinical criteria without other explanation for the illness (6).

Diagnosis criteria for KS:

A. Fever of at least 5 days' duration.

B. Presence of four of the following five conditions:

1) bilateral conjunctival injection;
2) changes of the mucosae of the oropharynx, including injected pharynx, injected and/or dry fissured lips and strawberry tongue;
3) changes of the peripheral extremities, such as edema and/or erythema

of hands and/or feet, and desquamation usually beginning periungually;

4) rash, primarily truncal; polymorphous but nonvesicular;
5) cervical lymphadenopathy.

C. Illness not explained by other known disease process.

Fever is generally high (40°C or higher), remittent and prolonged. The duration of fever is usually 1 to 2 weeks in untreated patients. It commonly resolves within 4 to 5 days of the institution of aspirin (50—100 mg/kg/day). Fever resolves significantly more promptly when intravenous γ-globulin (IVGG, single 2 g/kg dose) is administered with aspirin (7).

Conjunctival injection involves the bulbar conjunctivae much more severely than tha palpebral or tarsal one and is not associated with exudate. It usually begins shortly after the onset of fever and usually persists for 1 to 2 weeks. In patients treated with IVGG it may significantly improve almost immediately following treatment.

Changes in the mouth are characterized by erythema; dryness, fissuring, peeling and bleeding of the lips; erythema of the oropharyngeal mucosa; strawberry tongue with diffuse erythema and prominent papillae and lack of ulcerations.

The findings in the hands and feet are distinctive. Erythema of the palms and soles and/or firm induration of the hands and feet are present. It limits movements and may be painful. Desquamation of the fingers and toes begins in the periungual region and may extend to the palms and soles as well. Characteristically it is seen at days 10 to 20 after the onset of fever, but not in the first week of illness. Approximately 1 to 2 months later, deep transverse grooves across the nails (Beau's lines) may appear and subsequently grow out with the nail or occasionally a nail will be shed.

The rash usually appears within 5 days after the onset of fever and may take many forms: an urticarial exanthema with large erythematous plaques, a morbilliform maculopapular rash that may be multiform-like with target lesions, a scarlatiniform erythroderma or rarely a fine micropustular form. There is usually wide involvement of the trunk and extremities. Desquamation may occur in other areas in about 10% of patients, particularly in the perineal region.

Cervical lymphadenopathy is seen in 50% to 70%, whereas the other five criteria are observed in more than 90% of patients. At least one lymph node greater than 1.5 cm in diameter is necessary to fulfil this criterion. In patients usually over the age of 3 years cervical lymphadenopathy is the most striking clinical symptom and the other ones are often overlooked. Therefore, all clinical signs of KS should be sought in patients with cervical adenitis, particularly if it fails to improve following treatment with intravenous antibiotic therapy.

Associated features of KS are listed below:

1) extreme irritability, specially in infants;
2) arthralgia, arthritis;

3) aseptic meningitis;
4) cardiac disease;
5) hepatic dysfunction;
6) hydrops of the gallbladder;
7) diarrhea;
8) otitis media;
9) pneumonitis, mild, radiologically but not clinically apparent;
10) erythema and induration at site of the Calmette-Guerin bacillus inoculation.

The course of KS can be divided into three clinical phases. The acute febrile phase, usually lasting 7 to 14 days, is characterized by fever, conjunctival injection, mouth and lip changes, swelling and erythema of the hands and feet, rash, lymphadenopathy, aseptic meningitis, diarrhea and hepatic dysfunction. In the subacute phase fever, rash and lymphadenopathy resolve, but irritability, anorexia and conjunctival injection persist. Desquamation of the fingers and toes, arthritis and arthralgia, myocardial dysfunction and thrombocytosis are seen in this phase, which lasts from approximately day 10 to day 25 after the onset of illness. The convalescent stage begins when all clinical signs of illness have disappeared and continues until the sedimentation rate returns to normal, usually 6 to 8 weeks after the onset of illness.

LABORATORY FEATURES

The most characteristic is a moderate to marked leukocytosis with a predominance of neutrophils in the first week of illness. Normocytic, normochronic anemia without evidence of hemolysis or reticulocytosis occurs commonly and resolves spontaneously in the convalsecent phase. Elevation of the sedimentation rate is almost universal and can be very helpful in distinguishing KS from viral illnesses and drug reactions. Elevated C-reactive protein and erum α_1-antitrypsin levels are present with the onset of fever and persists for 6 to 8 weeks. The platelet count begins to rise in the second week of illness, peaking at about 3 weeks at a mean count of 800,000/mm^3. Total serum IgM and IgA concentrations are within normal limits, whereas IgG may be decreased and IgE usually moderately elevated (8). Laboratory findings are nonspecific and nondiagnostic in KS.

EPIDEMIOLOGY

KS is almost exclusively an illness of young children. About 80% of patients are under the age of 4 years and the syndrome is unusual after 8 years of age. KS occurs worldwide and affects children of all races with the Asians at the highest risk and the Caucasians at the lowest risk (9).

ETIOLOGY

The etiology of KS remains unknown. Many clinical and epidemiologic characteristics (acute onset with fever, rash, adenitis, exanthema, conjunctival involvement, age distribution, seasonal peaks in winter and spring, well-documented epidemics superimposed on endemic incidence) suggest an infectious etiology. However conventional bacterial and viral cultures, as well as extensive serologic investigations, have failed to identify a causative agent (10).

PATHOLOGY

Kawasaki's observations from 1973 of his 13 autopsy cases revealed that a periarteritis nodosa-like lesion is the pathologic hallmark of the disease and that coronary artery involvement with aneurysmal dilatation was the major pathologic manifestation (2). Subsequently it was proposed that lesions previously classified as infantile periarteritis nodosa (IPN) actually represented unrecognized KS (11). It is important for pediatric pathologist to consider coronary arteritis occurring in infants and young children to be highly suggestive of KS. When the clinical diagnostic criteria are met, the diagnosis is certain.

TREATMENT

Therapy for KS is aimed at reducing inflammation in the myocardium and in the coronary artery wall and at preventing thrombosis by inhibiting platelet aggregation. Current recommended regimen is presented below:

A. Acute stage:
   1) aspirin: 80—100 mg/kg/day in 4 divided doses until about day 14 of illness;
   2) intravenous γ-globulin (IVGG): 2 g/kg as a single dose given over 12 hrs.

B. Convalescent stage (after day 14 of illness in afebrile patient):
   1) aspirin: 3—5 mg/kg/day in a single dose; discontinue 6—8 weeks after onset of illness after verifying that no coronary abnormalities are present by echocardiography.

C. Chronic therapy for patients with coronary abnormalities:
   1) aspirin: 3—5 mg/kg/day in a single dose; dipyridamole in selected patients deemed to be at high risk;
   2) heparin with antiplatelet therapy in patients with particularly severe coronary findings or past evidence of coronary thrombosis.

D. Acute coronary thrombosis:
   1) fibrynolytic therapy with streptokinase, urokinase or tissue plasminogen activator under the supervision of a cardiologist.

Aspirin therapy should be interrupted if the patient develops varicella or influenza in order to reduce the risk of Reye's syndrome. Steroids should be contraindicated in KS (12, 13). IVGG for 5 days with aspirin is superior to aspirin alone with respect to the development od echocardiographic coronary abnormalities (14). It also reduces the prevalence of long-term coronary artery abnormalities (15). The dramatic antiinflammatory effect of IVGG on acute KS is frequently apparent within a few hours of the infusion (16). Therefore, single-dose IVGG at 2 g/kg with aspirin (80—100 mg/kg/day) is now the treatment of choice for patients with acute KS. The decision to treat patients with IVGG later than the 10th day of illness must be made on individual basis but it seems to be beneficial later in the course of illness as well.

Infants, particularly those under 6 months of age frequently lack full diagnostic criteria for KS. Unfortunately, these young infants with KS are also at extremely high risk of developing coronary artery abnormalities. Therefore, early diagnosis of acute KS and institution of appriopriate therapy are particularly important in this age group (17).

Patients with KS should undergo periodic physical examinations and complete blood cell counts, determinations of sedimentation rate and platelet counts until these return to normal. Liver function tests and an electrocardiogram may be useful in the first week of illness. Aneurysms are likely to be apparent in the third week after the onset of illness. If there are no abnormalities on echocardiography, it should be repeated about 1 month later. If this second study also fails to demonstrate an abnormality and the sedimentation rate and platelet count have returned to normal, aspirin is discontinued. If the patient has abnormal echocardiogram during the acute or convalescent stage, aspirin is continued. Low-dose aspirin is continued after resolving of aneurysms, since the endothelial lining may still be abnormal dispite return to a normal caliber. In patients with persistent small solitary aneurysm, long-term low-dose aspirin should be administered. In patients with large or multiple coronary aneurysms without obstruction, long-term antiplatelet drugs or anticoagulant therapy is recommended. Patients' activities should be restricted.

A difficult management problem in KS is the patient who develops obstructive changes in one or more coronary arteries. Small thrombi can be managed with oral anticoagulant therapy. Intracoronary or intravenous thrombolytic therapy, transluminal coronary angioplasty or coronary bypass grafting surgery are options for more advanced cases.

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STRESZCZENIE

Zespół Kawasaki jest chorobą małych dzieci o nieznanej etiologii. Po raz pierwszy opisano ją przed ponad 20 laty. U 20% nieleczonych dzieci dochodzi do rozwoju poważnych następstw w układzie sercowo-naczyniowym, które mogą być przyczyną zgonów. Leczenie koncentruje się na zmniejszeniu stanu zapalnego w naczyniach wieńcowych i zapobieganiu tworzeniu się zakrzepu. Dożylnie stosowana γ-globulina łącznie z kwasem acetylosalicylowym jest skuteczna w zapobieganiu rozwojowi choroby naczyń wieńcowych, jeżeli zostanie zastosowana odpowiednio wcześnie. Wzrost zachorowalności na tę chorobę powiększył liczbę małych dzieci z chorobą naczyń wieńcowych, czyniąc poznanie jej etiologii zadaniem o kluczowym znaczeniu dla poprawy rozpoznania i możliwości leczenia.